respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 15-20 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Examiner acknowledges that the specification while being enabling for *in vitro* inhibition of hematopoietic cell protein tyrosine kinase expression comprising administering antisense oligonucleotides that specifically target hematopoietic cell protein kinase nucleic acids does not reasonably provide enablement for *in vivo* antisense inhibition of hematopoietic cell protein kinase expression, nor any treatments or prevention of effects for conditions or diseases associated with hematopoietic cell protein kinase in organisms; the Examiner cites several articles on the technology of antisense to support this position. Applicants respectfully traverse this rejection.

Applicants disagree with the Examiner's suggestion that cited references support the position that application of antisense *in vivo* is highly unpredictable.

The Examiner has pointed to several articles and a press release on the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable. However, when one reads each of the papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed in cells in the instant invention would also occur in cells in animals and humans.

The paper by Crooke is a review paper on the basic principles of antisense therapeutics. The statements alluded to by the Examiner concerning extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are only one small part of this review paper. When read in its entirety the author is merely stating a well known fact in the development of any drug, not merely antisense. Pharmacokinetics is not the study of the pharmacological activity of an agent, such as is studied commonly in cells, but rather the study of the biological distribution of a drug in an animal or human. Therefore, the

statements by the author do not demonstrate the unpredictability of antisense oligos *in vivo* but rather merely state the obvious, that one would not use studies on cellular uptake to predict pharmacokinetics in animals or humans because it is not a logical use of such data for any drug. Data in cells are used routinely, however, as predictors of pharmacological activity in animals and humans. It is a fundamental principle of drug development that data from whole cell studies, such as are provided in Example 15 of the instant specification, are directly applicable to predicting *in vivo* activity. The teachings of the paper by Crooke and the other cited review paper (Branch) provide no reason to doubt that this fundamental principle is applicable to antisense agents.

In fact, statements in the paper by Crooke support the fact that development of antisense drug products is viewed by those of skill in the art as being the same as development of any other drug product in terms of applying the basic principles of pharmacology. For example, on page 22, first paragraph, Crooke points out "...numerous well-controlled [pharmacological] studies have been reported in which antisense activity was conclusively demonstrated [*in vitro*]." The key according to Crooke is the careful design of the *in vitro* studies to carefully evaluate dose-response

relationships and antisense mechanism, similar to the type of studies presented in the instant specification. Therefore, what this paper, and the other cited by the Examiner actually teach is that antisense oligonucleotides must be developed using well designed studies that progress logically from activity in cells to activity in animals and humans. Nowhere in the reference does the author state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*.

Moreover, the paper by Branch (1998) teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

The paper by Palu et al. (1999) is a review paper on the technology of gene therapy, not antisense. Gene therapy is an entirely different technology with its own set of issues for drug development. Citing this paper to support the unpredictability of antisense is inappropriate. Nowhere does this paper state that extrapolation from *in vitro* data on antisense compounds to *in vivo* effects is unpredictable.

The paper by Agrawal and Kandimalla (2000) is another review paper on the technology of antisense. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

The paper by Chirila et al. (2002) is a review of the use of polymers for delivery of antisense compounds. Although this paper reviews problems that have arisen during development of antisense, problems that are addressed and solved in the specification as filed, nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

Finally, the BioWorld article cited by the Examiner does not support the conclusion that data from *in vitro* studies is not predictive of *in vivo* activity. This failure of a clinical trial for Crohn's disease is a very different standard where a drug must be statistically significantly better than a placebo on a particular endpoint. It does not mean the drug was without activity to inhibit gene expression when results from *in vitro* studies are extrapolated to *in vivo* activity.

However, Applicants have amended claim 15 and canceled claims 16-20 in an earnest effort to advance the prosecution and facilitate the allowance of this case. Applicants reserve the right

to file a continuing application directed to this subject matter without prejudice. Withdrawal of the rejection is requested in light of these amendments.

II. Rejection of Claims Under 35 U.S.C. 102(b)

Claims 1, 2, 4, 5, 11, 12, 14 and 15 have been rejected under 35 U.S.C. 102(b) as being anticipated by Wei et al. (1996). The Examiner suggests that this paper discloses methods and compositions comprising antisense compounds 8 to 50 mer that target and inhibit expression of SEQ ID NO: 3 which encodes hematopoietic cell protein kinase, as well as compositions that comprise a pharmaceutically acceptable carrier. Applicants respectfully traverse this rejection.

At the outset, Applicants have amended claim 1, and by dependency claims 2-15, to refer to antisense compounds targeted to specific regions of particular hematopoietic cell protein kinase nucleic acid molecules that are recited by SEQ ID NO. Support for these amendments can be found throughout the specification as filed but in particular at pages 81-85.

Wei et al. (1996) disclose a 20 mer phosphorothioate oligonucleotide targeting the start codon of human hematopoietic cell protein kinase. Nowhere does this patent teach or suggest

antisense compounds that target any other specific region of hematopoietic cell protein kinase nucleic acid molecules as now claimed, which does not include the start codon region. Accordingly, this paper fails to teach the limitations of the claims as amended and cannot anticipate the instant invention (MPEP 2131). Withdrawal of this rejection is respectfully requested.

Claims 1, 2 and 11 have been rejected under 35 U.S.C. 102(b) as being anticipated by Matsubara et al. (WO 95/14772 A1). The Examiner suggests that this patent application teaches an antisense compound 8 to 50 nucleobases in length which targets and inhibits expression of hematopoietic cell protein kinase encoded by SEQ ID NO: 3. Applicants respectfully disagree with the Examiner's conclusions regarding this reference.

In Matsubara et al. (WO 95/14772), the nucleic acid sequence alignment provided appears to show nucleotides 1673-1692 of the human hematopoietic cell protein tyrosine kinase sequence (SEQ ID NO: 3), nucleotides that are the same as nucleotides 1-20 of the other sequence shown (indicated as Db). However, the nucleotides are in the opposite orientation (3' to 5') along the same strand and are not complementary as suggested by the Examiner. Thus, the two sequences are neither complementary nor identical but merely a reverse one of the other. As a result, the cited sequence would

not hybridize with SEQ ID NO: 3 of the instant invention as suggested by the Examiner. Further, it is also unclear to Applicants whether the Db sequence is a 20 mer or merely a 20-nucleobase portion of a much larger (> 50 nucleobase) sequence. Accordingly, the Matsubara et al. reference cannot anticipate the instant invention as it fails to teach a compound which specifically hybridizes with and inhibits the expression of hematopoietic cell protein kinase. Withdrawal of this rejection is respectfully requested.

Claims 1, 2 and 4-14 have been rejected under 35 U.S.C. 102(b) as being anticipated by McKay et al. (US Patent 5,877,309). The Examiner suggests that this patent discloses compositions comprising antisense compounds that specifically hybridize with and inhibit expression of SEQ ID NO: 3, including the claimed modifications. The Examiner has pointed specifically to sequence alignment data for SEQ ID NO: 31 of McKay et al. Applicants respectfully traverse this rejection.

McKay et al. (US Patent 5,877,309) disclose antisense compounds targeted to JNK. There is a 17 nucleobase overlap between SEQ ID NO:31 of McKay et al. and SEQ ID NO: 56 of the instant invention. However, SEQ ID NO: 56 was inactive in the instant invention as shown at Table 1, page 83 of the specification as

filed. Therefore, this reference cannot anticipate the instant invention as it fails to teach the limitations of the claims as filed which are drawn to antisense compounds targeted to hematopoietic cell protein kinase that are capable of inhibiting expression of hematopoietic cell protein kinase. Moreover, the claims have been amended, as discussed *supra* to, recite antisense targeted to specific regions of hematopoietic cell protein kinase nucleic acid molecules, which is also not taught or suggested by this reference. Accordingly, withdrawal of this rejection is respectfully requested.

III. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1, 2 and 4-15 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Wei et al., McKay et al., and Matsubara et al., in view of Quintrell et al. (1987), Lichtenberg et al. (1992), and Milner et al. (1997). The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill to inhibit expression of human hematopoietic cell protein kinase because the McKay et al. and Milner et al. teach antisense inhibition of genes with known sequences, because the sequence of hematopoietic cell protein kinase was known, and because Quintrell et al. and Lichtenberg et al. teach the role of hematopoietic cell

protein kinase in cellular differentiation and neoplastic transformation, which is motivation for the instant invention. The Examiner suggests that an expectation of success is provided but does not point to any of the specific references listed for support. Applicants respectfully traverse this rejection.

At the outset, claim 1 and its dependent claims have been amended to recite antisense compounds targeted to specific regions of nucleic acid molecules encoding hematopoietic cell protein kinase. Support for these amendments can be found throughout the specification as filed, but in particular at pages 81-85.

The primary references cited have been discussed in detail *supra* (Wei et al., McKay et al., and Matsubara et al.). None of these references, either alone or combined, teach or suggest the limitations of the claims as amended which recite targeting specific regions of specific hematopoietic cell protein kinase nucleic acid molecules with antisense.

The secondary references cited fail to overcome the deficiencies in teaching of the primary references.

Milner et al. teach a method for identifying antisense oligonucleotides using optimization techniques where the antisense oligonucleotides have 1-17 bases and target sequences of a gene. However, nowhere does this paper teach or suggest antisense

oligonucleotides 8 to 50 nucleobases in length targeted to hematopoietic cell protein kinase, or any region of a hematopoietic cell protein kinase nucleic acid molecule.

Quintrell et al. (1987) disclose the cloning of human hematopoietic cell protein kinase. Although the sequence of the gene may be taught by this reference, nowhere does this reference teach or suggest antisense oligonucleotides 8 to 50 nucleobases in length targeted to hematopoietic cell protein kinase, or any region of a hematopoietic cell protein kinase nucleic acid molecule.

Lichtenberg et al. (1992) disclose that the expression of hematopoietic cell protein kinase is highest in differentiated monocytic and granulocytic cells indicating the protein may function in myeloid differentiation or activation. However, nowhere does this paper teach or suggest antisense oligonucleotides 8 to 50 nucleobases in length targeted to hematopoietic cell protein kinase, or any region of a hematopoietic cell protein kinase nucleic acid molecule.

Therefore, even when combined, these secondary references fail to overcome the deficiencies in teaching of the primary references.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in

the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly, the combination of prior art cited fails to teach or suggest the limitations of the claims as amended, which claim antisense compounds targeted to specific regions of nucleic acid molecules encoding hematopoietic cell protein kinase, and thus cannot render the instant claimed invention obvious. Withdrawal of this rejection is therefore respectfully requested.

IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attorney Docket No.: RTS-0345
Inventors: Borchers and Dobie
Serial No.: 10/007,010
Filing Date: December 4, 2001
Page 15

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**."

Respectfully submitted,

Jane Massey Licata
Registration No. 32,257

Date: **January 27, 2003**

Licata & Tyrrell P.C.
66 E. Main Street
Marlton, New Jersey 08053

(856) 810-1515

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 11 and 16-20 have been canceled without prejudice.

Claims 1 and 15 have been amended as follows:

1. (twice amended) A compound 8 to 50 nucleobases in length targeted to a 5'-untranslated region, a coding region, a stop codon region, or a 3'-untranslated region of a nucleic acid molecule ~~encoding hematopoietic cell protein tyrosine kinase~~ of ~~(~~SEQ ID NO: 3~~)~~ encoding hematopoietic cell protein tyrosine kinase, or an intron 5 region, an intron:exon junction region, or an intron 9 region of a nucleic acid molecule of SEQ ID NO: 10 encoding hematopoietic cell protein tyrosine kinase, wherein said compound specifically hybridizes with ~~said nucleic acid molecule encoding hematopoietic cell protein tyrosine kinase~~ one of said regions and inhibits the expression of hematopoietic cell protein tyrosine kinase.

15. (amended) A method of inhibiting the expression of hematopoietic cell protein tyrosine kinase in cells or tissues comprising contacting ~~said~~ cells or tissues *in vitro* with the

antisense compound of claim 1 so that expression of hematopoietic cell protein tyrosine kinase is inhibited .